



NOTES

AMINO ACID METABOLISM DISORDERS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Inherited disorders of amino acid metabolism, transportation, excretion
- Impaired enzymes → reactant accumulation → toxicity
- Inherited autosomal/X-linked recessive

CAUSES

- Gene mutation

RISK FACTORS

- Infants with central nervous system (CNS) disorders most commonly affected

SIGNS & SYMPTOMS

- See individual disorders

DIAGNOSIS

LAB RESULTS

- Amino acids levels in blood, urine

TREATMENT

OTHER INTERVENTIONS

- Modified diet

ALKAPTONURIA

osms.it/alkaptonuria

PATHOLOGY & CAUSES

- Inherited autosomal recessive disorder of tyrosine, phenylalanine metabolism with build-up of degradation product (homogentisic acid) in connective tissues
- Homogentisic acid transforms into polymer → deposition of polymer into collagen fibers of connective tissues (e.g. cartilage) → ochronosis

CAUSES

- Mutation of homogentisic oxidase gene (HGO) → deficit of homogentisate oxidase → ↑ homogentisic acid

COMPLICATIONS

- Coronary artery disease
- Arthritis
- Renal stones

SIGNS & SYMPTOMS

- Usually asymptomatic in childhood/adolescence
- In infants, urine in diapers darkens due to oxidation of homogentisic acid; "black nappies"
- Bluish pigmentation of sclera, ear, etc.
- Pain in spine, hip, knee joints

VISIT...

LANZAROTE
Caliente.COM

DIAGNOSIS

DIAGNOSTIC IMAGING

Radiology

- Calcification of multiple intervertebral discs

LAB RESULTS

- Dark brown/black color of urine on prolonged air exposition
- Chromatography
 - ↑ homogentisic acid

TREATMENT

MEDICATIONS

- Herbicide nitisinone → inhibits enzyme which converts tyrosine to homogentisic acid → ↓ homogentisic acid

OTHER INTERVENTIONS

- Tyrosine, phenylalanine restriction → ↓ homogentisic acid excretion



Figure 40.1 An X-ray image demonstrating calcification of the intervertebral discs in an individual with ochronosis.



Figure 40.2 Alkaptonuria leads to the accumulation of homogentisic acid giving the clinical appearance known as ochronosis.

CYSTINURIA

osms.it/cystinuria

PATHOLOGY & CAUSES

- Autosomal recessive disorder; high levels of cystine in urine → kidney, ureter, bladder stones

CAUSES

- Mutation of *SLC3A1*, *SLC7A9* gene → defect of intestinal, renal amino acid transporter affecting positively charged amino acids (e.g. cysteine, arginine, ornithine)

COMPLICATIONS

- Hydronephrosis, pyelonephritis, frequent urinary tract infections (UTIs)

SIGNS & SYMPTOMS

- May be asymptomatic
- Flank pain, hematuria

DIAGNOSIS

LAB RESULTS

- Sodium cyanide-nitroprusside test
 - Determination of cystine concentration
- Urinalysis
 - Pathognomonic hexagonal crystals
- Stone analysis

TREATMENT

MEDICATIONS

- Chelation therapy with penicillamine
 - Forming soluble disulfide complex

OTHER INTERVENTIONS

- Sufficient hydration; urine alkalization
- Protein, sodium restriction
- Formed stones
 - Renal:** extracorporeal shock wave lithotripsy (ESWL)
 - Ureteric:** intracorporeal lithotripsy
 - Bladder:** cystolitholapaxy

HARTNUP DISEASE

osms.it/hartnup-disease

PATHOLOGY & CAUSES

- Inherited autosomal recessive metabolic disorder affecting neutral amino acids (esp. tryptophan)

CAUSES

- Intestinal, renal deficiency of neutral amino acid transporters → ↓ absorption from

intestines, ↓ reabsorption from kidneys → less amino acids available to build proteins

COMPLICATIONS

- Drop of tryptophan to niacin conversion → decrease of nicotinamide, NAD^+ → pellagra-like symptomatology
- Hyper/hypopigmentation in repeated sunlight exposure

SIGNS & SYMPTOMS

- Pellagra-like symptoms
- Photosensitivity
- Diarrhea
- Nervous system symptoms (e.g. ataxia, tremor, headaches; intellectual disability, mental abnormalities)
- Ocular manifestations (e.g. nystagmus, double vision)

DIAGNOSIS

LAB RESULTS

- Urine chromatography
 - Increased levels of neutral amino acids (e.g. aminoaciduria)

TREATMENT

OTHER INTERVENTIONS

- High-protein diet, nicotinic acid supplements, sunlight protection

HOMOCYSTINURIA

osms.it/homocystinuria

PATHOLOGY & CAUSES

- Autosomal recessive disorder; high levels of homocysteine in blood, urine due to impaired methionine metabolism

TYPES

- Type I
 - Deficiency of cystathionine synthase
- Type II
 - Deficiency of methionine synthase
- Type III
 - Cystathionine synthase impairment → decreased affinity for pyridoxal phosphate

COMPLICATIONS

- Increased risk for thrombotic strokes

SIGNS & SYMPTOMS

- Ocular anomalies (e.g. myopia, ectopia lentis)
- Marfan-like presentation
- Intellectual disability
- Cardiovascular defects
- Osteoporosis

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan, MRI

- Large-vessel/lacunar stroke

LAB RESULTS

- Blood, urine quantitative test for homocystinuria
- Cyanide nitroprusside test
 - Urine screening test for amino acids containing sulfur
- Measurement of cystathionine synthase activity in cultured fibroblasts

TREATMENT

OTHER INTERVENTIONS

- Vitamin B₆, B₁₂, folate acid supplements in cystathionine synthase deficiency
- Methionine in methionine synthase deficiency
- Cysteine, high doses of vitamin B₆ in decreased affinity of cystathionine synthase for pyridoxal phosphate

MAPLE SYRUP URINE DISEASE

osms.it/maple-syrup-urine-disease

PATHOLOGY & CAUSES

- Disease caused by **impaired metabolism of branched amino acids** (e.g. isoleucine, leucine, valine); AKA branched-chain ketoaciduria
- **Autosomal recessive** inheritance
- Impaired metabolism → **accumulation of byproducts** with toxicity in brain, other organs

TYPES

Classic MSUD

- Most common; occurs soon after birth

Non-classic MSUD

- Later onset, less severe symptoms

CAUSES

- Mutation of genes *BCKDHA*, *BCKDHB*, *DBT* → dysfunction of enzyme complex

COMPLICATIONS

- Possible permanent **brain damage**
- **Fatal** if not treated in first five months

SIGNS & SYMPTOMS

- **Sweet** (maple syrup-like) **smelling urine**

Classic MSUD

- Healthy-looking infants at birth, quick deterioration; **feeding difficulties**, failure to thrive (FTT), vomiting, seizures

Non-classic MSUD

- **Vomiting**, diarrhea, rapid neurological decline, ataxia, seizures, coma

DIAGNOSIS

LAB RESULTS

- Plasma amino acid test
 - Alloisoleucine detection
- Prenatal diagnostic by measuring enzyme activity in cultured amniocytes

OTHER DIAGNOSTICS

- Genetic testing
 - *BCKDHA*, *BCKDHB*, *DBT*
- Physical examination, newborn screening

TREATMENT

SURGERY

- Liver transplant

OTHER INTERVENTIONS

- Regular metabolism check
- **Regulation of isoleucine, leucine, valine intake**

ORNITHINE TRANSCARBAMYLASE DEFICIENCY

osms.it/OTC-deficiency

PATHOLOGY & CAUSES

- X-linked disorder affecting ornithine transcarbamylase enzyme
- Disorder of urea cycle → accumulation nitrogen in form of ammonia
- Defect of ornithine transcarbamylase enzyme → carbamoyl phosphate accumulation → conversion of carbamoyl phosphate into orotic acid
- Presents often in neonatal form, may present later

RISK FACTORS

- Individuals who are biologically male fully affected due to X-recessive transmission
- Individuals who are biologically female usually asymptomatic

SIGNS & SYMPTOMS

- Neonatal form
 - Lethargy, irritability, poor feeding, seizures, impaired thermoregulation; hyperventilation → respiratory alkalosis; cerebral edema, possible progression into coma, death
- Later presentation
 - Headaches, nausea, vomiting, psychiatry disorders

DIAGNOSIS

LAB RESULTS

- Plasma, urine amino acid analysis
 - Elevated arterial/venous ammonia (hallmark finding), orotic acid, glutamine
 - Decreased blood urea nitrogen (BUN), citrulline concentrations
- Urine organic acid analysis
 - Orotic acid in urine

OTHER DIAGNOSTICS

- Ornithine transcarbamylase only expresses in liver; liver biopsy needed to confirm diagnosis
- Newborn screening

TREATMENT

SURGERY

- Liver transplant

OTHER INTERVENTIONS

- Low-protein diet
- Nitrogen scavenging agents
 - Sodium benzoate, arginine

PHENYLKETONURIA

osms.it/phenylketonuria

PATHOLOGY & CAUSES

- Genetic disorder characterized by high levels of phenylalanine
- Autosomal recessive inheritance

CAUSES

- PAH gene mutation → hepatic phenylalanine hydroxylase deficiency → defect in metabolism of phenylalanine → activation of alternative pathways → accumulation of phenylalanine, byproducts
- Mutation of HPABH₄ genes → impairment in synthesis, recycling of tetrahydrobiopterin cofactor (BH₄) → impaired function of phenylalanine hydroxylase enzyme

COMPLICATIONS

- If untreated
 - Severe intellectual disability
- Seizures
- Increased risk of anxiety, inattention, depression, other neuropsychiatric disorders
- Phenylalanine embryopathy
 - Inappropriate diet during pregnancy in individuals with phenylketonuria → elevated levels of phenylalanine concentration in serum → teratogenic effects of phenylalanine passing placenta → newborn with microcephaly, mental disorders, congenital heart defects

SIGNS & SYMPTOMS

- Skin, hair pigmentation disorders (lack of melanin pigment)
- Eczema
- Musty odor

DIAGNOSIS

LAB RESULTS

Cranial magnetic resonance spectrometry

- Brain phenylalanine levels

Chromatography/tandem mass spectrometry

- ↑ phenylalanine

Guthrie test

- Formerly used; replaced with tandem mass spectrometry

Ferric chloride urine test

- Rarely used; results may be negative in first months of life

OTHER DIAGNOSTICS

- Newborn screening



Figure 40.3 The heelprick test is performed on all newborn babies and screens for phenylketonuria.

TREATMENT

MEDICATIONS

- Sapropterin

OTHER INTERVENTIONS

- Lifelong low-phenylalanine diet with tyrosine supplements
- Avoid artificial sweeteners containing phenylalanine (e.g. aspartame)